

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review article

Identification and diagnosis of patients with familial chylomicronaemia syndrome (FCS): Expert panel recommendations and proposal of an “FCS score”



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ARTICLE INFO

Article history:

Received 29 March 2018

Received in revised form

23 May 2018

Accepted 13 June 2018

Available online 18 June 2018

Keywords:

Familial chylomicronaemia syndrome

Major hypertriglyceridaemia

Multifactorial chylomicronaemia

Acute pancreatitis

ABSTRACT

Familial chylomicronaemia syndrome (FCS) is a rare, inherited disorder characterised by impaired clearance of triglyceride (TG)-rich lipoproteins from plasma, leading to severe hypertriglyceridaemia (HTG) and a markedly increased risk of acute pancreatitis. It is due to the lack of lipoprotein lipase (LPL) function, resulting from recessive loss of function mutations in the genes coding LPL or its modulators. A large overlap in the phenotype between FCS and multifactorial chylomicronaemia syndrome (MCS) contributes to the inconsistency in how patients are diagnosed and managed worldwide, whereas the incidence of acute hypertriglyceridaemic pancreatitis is more frequent in FCS. A panel of European experts provided guidance on the diagnostic strategy surrounding FCS and proposed an algorithm-based diagnosis tool for identification of these patients, which can be readily translated into practice. Features included in this FCS score comprise: severe elevation of plasma TGs (fasting TG levels >10 mmol/L [885 mg/dL] on multiple occasions), refractory to standard TG-lowering therapies, a young age at onset, the lack of secondary factors (except for pregnancy and oral oestrogens) and a history of episodes of acute pancreatitis. Considering 53 FCS patients from three cohorts and 52 MCS patients from three cohorts, the overall sensitivity of the FCS score (≥ 10) was 88% (95% confidence interval [CI]: 0.76, 0.97) with an overall specificity of 85% (95% CI: 0.75, 0.94). Receiver operating characteristic curve area was

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0.91. Pragmatic clinical scoring, by standardising diagnosis, may help differentiate FCS from MCS, may alleviate the need for systematic genotyping in patients with severe HTG and may help identify high-priority candidates for genotyping.

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1. Introduction

1.1. Key issues in the identification and diagnosis of familial chylomicronaemia syndrome

Familial chylomicronaemia syndrome (FCS) is a rare, inherited disorder of triglyceride (TG)-rich lipoprotein metabolism [1]. The estimated worldwide prevalence is approximately one individual per million [2]. It often presents in childhood and has been described in all ethnicities, although a higher prevalence has been observed in some geographical areas such as Quebec, due to a founder effect [3].

Chylomicronaemia is the accumulation in the bloodstream of chylomicrons, i.e., large, TG-rich lipoprotein particles produced by enterocytes after a meal [1,2]. Under physiological conditions, chylomicrons are rapidly cleared from plasma by the action of lipoprotein lipase (LPL), an enzyme located on the endothelial surface of adipose and muscle tissues, which hydrolyses TG into fatty acids and glycerol. Chylomicrons are converted into chylomicron remnants, which are in turn taken up by specific cellular receptors [4]. In FCS, a lack of LPL functionality, mostly due to pathogenic variants in the set of genes involved in LPL function, markedly impairs clearance of chylomicrons from the plasma. The initial reports of FCS involved homozygous or compound heterozygous carriers of loss of function mutations in *LPL* and apolipoprotein C2 (*APOC2*) genes. Subsequently, combined loss of function mutations in genes coding for apolipoprotein A5 (*APOA5*), lipase maturation factor 1 (*LMF1*), glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (*GPIHBP1*) and glycerol-3-phosphate dehydrogenase 1 (*G3PDH1*) were also identified as causal in FCS [1,5–11]. Additional genes are likely to be identified in the future, since in a large proportion of patients (more than one-third) with a phenotype similar to FCS, no deleterious variants in the aforementioned genes can be identified [12,13].

Although environmental factors increase the magnitude of hyperchylomicronaemia, they are not required for the expression of FCS phenotype; however, many cases of FCS syndrome in women are discovered at the third trimester of pregnancy. It has been consistently reported that FCS strongly increases the risk of acute pancreatitis (AP) [14]. However, it remains an elusive goal to identify patients with FCS who will develop AP versus those who will not.

A key concern is that a clear diagnosis might be missed in patients with FCS. Indeed, the condition is very rare and high levels of TGs are more often due to multifactorial chylomicronaemia syndrome (MCS) [8,15]. This syndrome results from the combination, in various proportions, of predisposing variants ranging from loss of function heterozygous mutations to likely pathogenic variants in candidate genes with co-morbidities known to raise plasma TGs (uncontrolled diabetes, hypothyroidism, pregnancy) and environmental factors (such as alcohol abuse, unhealthy diet) and certain medications (such as glucocorticoids, ethinylestradiol, neuroleptics). MCS is also characterised by an increased risk of AP but the estimated odds ratio of 50 is clearly less than the AP odds ratio of 360 reported in patients with FCS (Fig. 1) [16,17].

The apparently similar phenotype of MCS means that FCS may

be missed or undiagnosed. Many patients with FCS suffer recurrent episodes of AP before the diagnosis is made. Lack of disease awareness on the part of physicians in emergency medicine, primary care and gastroenterology is a key barrier to FCS diagnosis, leading to a low rate of appropriate referrals and follow-up.

A panel of European clinical experts experienced in diagnosing FCS convened in Amsterdam in July 2017 to discuss the definition and terminology of FCS and optimal strategies for the identification, diagnosis and evaluation of patients, which could be readily translated into practice to improve the approach used to identify and diagnose FCS, which we present below.

2. Challenges in defining FCS

- FCS is characterised by very high plasma TG concentrations (>10 mmol/L or 885 mg/dL in the untreated state). A key characteristic is milky looking plasma, whereby a white chylomicron layer floats above the lactescent plasma compartment following decantation and/or low-speed centrifugation of the plasma sample. Although controversial [2], the expert panel considered that most adult patients with FCS present with both increased chylomicrons and very low-density lipoproteins (VLDLs), and, consequently, more often display type V than type I dyslipidaemia [9,18,19]. Therefore, type I phenotype has been considered to be poorly sensitive but a highly specific feature of FCS in adults. Type I phenotype is more frequently found in children with FCS, which may reflect the ability of hepatic lipase to efficiently hydrolyse VLDL-TG in children and teenagers [20]. It is noteworthy that few patients with auto-immune hyperchylomicronaemia also present with type I phenotype [5,21].
- Patients with FCS may experience physical complications including abdominal pain, which can range in intensity from mild to incapacitating [1]. Moreover, they have a high risk of developing severe recurrent AP [22,23], a potentially life-threatening complication [24], resulting in increased morbidity and mortality [2,25], and may lead to chronic pancreatitis, permanent damage to pancreatic tissue, pancreatic insufficiency and type 3 diabetes [26,27]. Studies have highlighted a significant relationship between TG level and pancreatitis, with a 4% increased risk of AP for every 100 mg/dL or ~1.1 mmol/L increase in TG level [28,29]. In a prospective cohort study, even mild hypertriglyceridaemia (HTG) (non-fasting TG > 177 mg/dL [2 mmol/L]) was associated with a graded increased risk of AP [30].
- Other clinical symptoms include transient eruptive xanthomas, which affect <50% of individuals with FCS, often appearing on the trunk and extremities, and lipemia retinalis, a milky appearance of the retinal vessels [1,29]. Hepatosplenomegaly may also result from TG uptake by macrophages [1]. Neurological symptoms, such as irritability, memory problems, dementia and depression, have also been documented [24]. Patients with FCS tend to have a lower body weight because of restriction of their food intake owing to abdominal pain. The impact of the disease is such that quality of life and daily activities including work may be adversely affected [31,32].

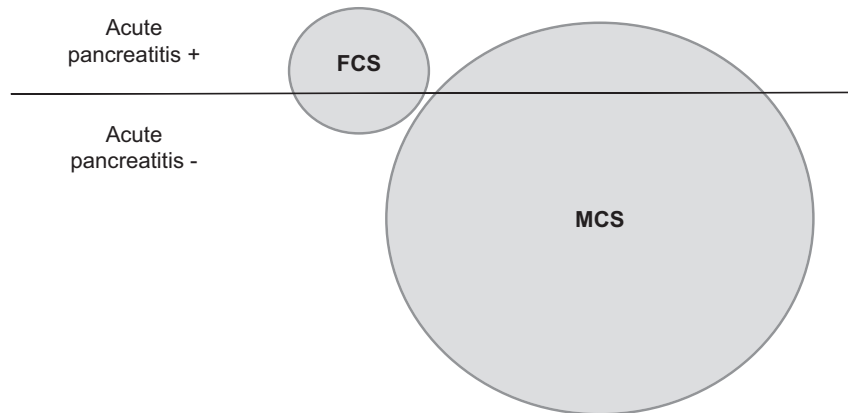


Fig. 1. Relative prevalence of pancreatitis in FCS and MCS.

Since the prevalence of MCS is much higher than FCS, although hypertriglyceridaemic acute pancreatitis relative risk is much less in MCS, the contribution of FCS and MCS to the overall incidence of pancreatitis cases is likely to be similar. FCS, familial chylomicronaemia syndrome; MCS, multifactorial chylomicronaemia syndrome.

We discussed the importance of using consistent, clear and well-defined terminology when describing the condition, ensuring that this is something that will be easily identified by patients, clinical chemists and primary care physicians, in addition to specialists more familiar with the area. Of the numerous terms that have been used historically in the literature, in the clinical setting and by patient societies, use of “FCS” seems to be a pragmatic choice. Indeed, there are key patient organisations that are using this terminology, including the LPLD Alliance (<http://www.lpldalliance.org/>) in the UK and The FCS Foundation (<https://www.livingwithfcs.org/>) in the USA. The condition should be characterised as a ‘syndrome’ due to the variety of symptoms present, with different presentations between individuals. The main limitation is that most of the cases are apparently sporadic, within a nuclear family, due to the recessive character of the disease. However, the preferred terminology is “familial chylomicronaemia syndrome” – abbreviated as “FCS”.

3. Diagnosis

3.1. Disease classification

One of the main difficulties that we considered is the uncertain boundary between FCS and MCS, since the genetic load increases progressively from MCS, where it can be minimal, to FCS, where it is maximal in carriers of homozygous nonsense mutations in the *LPL* gene. The full spectrum is described in Fig. 2. We propose that FCS corresponds to a monogenic disorder with a genetic load high enough to generate constant HTG, mostly >10 mmol/L (885 mg/dL) with recurrent decompensations in the absence of obvious secondary factors (and decreased post-heparin LPL activity, although infrequently assayed in clinical practice). In addition to homozygous *LPL* deficiency, homozygous loss of function mutations in *APOC2*, *APOA5*, *GPIHBP1*, *LMF1* and *G3PDH1* genes should be considered, as well as compound heterozygous mutations involving *LPL* and these genes.

Patients with MCS may have a combination of a heterozygous loss of function mutation and/or likely pathogenic frequent variants in TG-raising genes, thus producing (oligogenic/polygenic) severe HTG [8,9]. However, in such cases, hyperchylomicronaemia is often transient and low LPL activity is inconstant. Between recurrent decompensations, these patients mostly present with mild HTG. This phenotype is often observed in heterozygous *APOA5* loss of function mutations combined with various combinations of variants such as Haplotype Apo AV*2 and Apo AV*3 [33–35]. Between

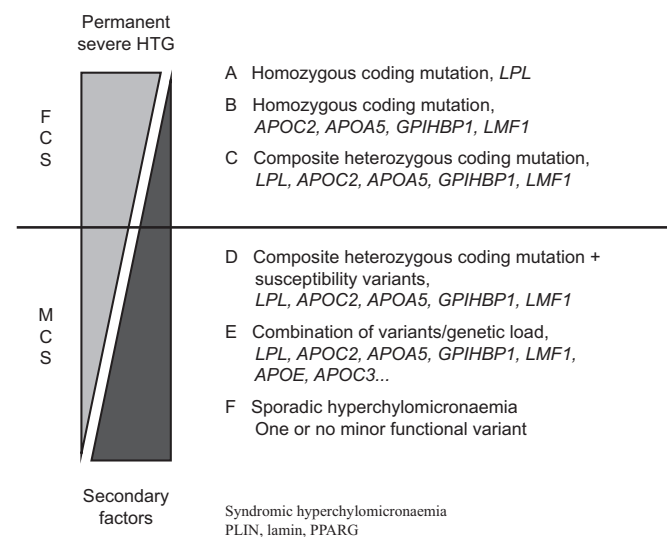


Fig. 2. Genetic load in FCS versus MCS.

FCS, familial chylomicronaemia syndrome; MCS, multifactorial chylomicronaemia syndrome; *LPL*, lipoprotein lipase; *APOC2*, apolipoprotein C2; *APOA5*, apolipoprotein A5; *GPIHBP1*, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; *LMF1*, lipase maturation factor 1; *APOE*, apolipoprotein E; *APOC3*, apolipoprotein C3; *PPARG*, peroxisome proliferator-activated receptor gamma.

decompensations, whereas plasma TG levels have partially decreased, post-heparin LPL activity is found to be normal 10 min after injection but is decreased in many patients 60 min after injection. This finding supports the hypothesis that some patients with MCS might have subtle alterations of LPL bioavailability [36]. Additionally, the apolipoprotein E2 allele is over-represented in patients with MCS; it is likely that the E2 allele contributes to decreases in hepatic chylomicron remnant clearance in patients carrying additional pathogenic variants known to alter LPL activity [15,37]. However, hyperchylomicronaemia is unusual even in E2/E2 patients, and they should be considered as suffering from MCS rather than FCS.

3.2. Pivotal features needed for an appropriate diagnosis of FCS

Differentiation of FCS from MCS is difficult, since the clinical and biological phenotype might be similar on decompensations. A number of parameters should be taken into consideration, given

the fact that the post-heparin LPL activity assay we mentioned above is not commonly used in clinical practice, and that both FCS and MCS share mostly the same type V lipid phenotype. Therefore, TG levels over time, clinical signs and history must be all be considered for establishing a diagnosis of FCS. Although arbitrary, our proposed cut-off TG level for FCS diagnosis is fasting TG levels >10 mmol/L or 885 mg/dL. This is supported by a study of Italian patients with monogenic HTG, in which the lowest TG levels reported were ~10 mmol/L [12].

It is advisable to check for a chylomicron layer by keeping plasma samples overnight when centrifugation is not able to provide evidence for a creamy layer. Screening for chylomicrons by agarose gel electrophoresis (lipidogram) is not reliable, since the largest chylomicrons often cannot enter the gel and consequently are not consistently detected. A TG/total cholesterol ratio >5 (mg/mg) > 2.2 (mmol/mmol) and a plasma apolipoprotein B concentration <100 mg/dL when plasma TG is > 10 mmol/L strongly support the presence of a high amount of chylomicrons and very large VLDL and remnants.

When the LPL activity assay can be performed (10 min after IV heparin injection [50 IU/kg]), LPL activity is found to be drastically decreased in homozygous LPL FCS and often lowered in cases of homozygous or compound heterozygous loss of function mutations in *APOC2*, *APOA5*, *GPIHBP1* and *LMF1* (Table 1). Reproducible increases of plasma TG > 10 mmol/L (885 mg/dL) over several weeks or months is a relevant criterion supporting diagnosis of FCS. Plasma TG levels in MCS have more variability and are much more sensitive to dietary and/or fibrate treatment, whereas in FCS, TG concentration is minimally improved with these measures.

In addition to the lipid phenotype, some clinical features also support the diagnosis of FCS, rather than the more common MCS. FCS occurs in younger patients, mostly without secondary factors, except for pregnancy and contraceptive oral oestrogen use, whereas MCS typically occurs in overweight adult patients with metabolic syndrome. Moreover, the occurrence of AP is more frequent in FCS than in MCS due to the partial response to a low-fat diet and higher plasma TG concentrations [38,39].

Next-generation sequencing is likely to facilitate the diagnosis of FCS, since all the candidate genes can be tested in the same run. However, due to its cost and paucity in core laboratories, not all clinicians have access to genetic assessment.

We propose a pragmatic diagnostic score for FCS (Fig. 3), which might help to distinguish between FCS and MCS, based on eight biological/clinical items, including the history of plasma TG concentration, the lack of secondary factors (except for pregnancy and oestrogenic oral contraceptives), history of AP, no history of familial combined hyperlipidaemia [40] and age at the first onset of symptoms. A low weight was given to history of AP, since it is not specific to FCS versus MCS, although it seems to be more frequent in FCS. In addition, a large proportion of young patients with FCS do not yet have history of AP and would be excluded if the score gives too much weight to this item.

Table 1
Phenotypes in FCS.

	<i>LPL</i>	<i>APOC2</i>	<i>APOA5</i>	<i>GPIHBP1</i>	<i>LMF1</i>	Anti-LPL/GPIHBP1 auto-antibodies ^a
Transmission	Recessive	Recessive	Co-dominant?	Recessive	Recessive	Sporadic
Variability of expressivity	+	++	++++	++	+++	Hectic
Initiation	Early	Early	Variable	Variable	Variable	Adult
Therapeutic resistance	+++	±	+++/+	+++	?	+++
Relative frequency in FCS	35–50% ^a	5%	10%?	5%	1%	<1%

FCS, familial chylomicronemia syndrome; *LPL*, lipoprotein lipase; *APOC2*, apolipoprotein C2; *APOA5*, apolipoprotein A5; *GPIHBP1*, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; *LMF1*, lipase maturation factor 1.

^a Relative frequency may be high in an area with a strong founder effect.

Recruitment phase

Severe primary HTG (fasting TGs >10 mmol/L or 885 mg/dL)

Patient pre-selection in non-acute setting

1. Fasting TGs >10 mmol/L for 3 consecutive blood analyses (+5)^a
 - Fasting TGs >20 mmol/L at least once (+1)
2. Previous TGs <2 mmol/L (-5)
3. No secondary factor^b (except pregnancy^c and ethinylestradiol) (+2)
4. History of pancreatitis (+1)
5. Unexplained recurrent abdominal pain (+1)
6. No history of familial combined hyperlipidaemia (+1)
7. No response (TG decrease <20%) to hypolipidaemic treatment (+1)
8. Onset of symptoms at age:
 - <40 years (+1)
 - <20 years (+2)
 - <10 years (+3)

FCS score:
≥10: FCS very likely
≤9: FCS unlikely
≤8: FCS very unlikely

Fig. 3. A practical diagnostic scoring system for FCS.

Numbers in parentheses = weighting given to the presence of each item. FCS score = the sum of all items present. FCS, familial chylomicronaemia syndrome; HTG, hypertriglyceridaemia; TG, triglyceride. ^a Plasma TG concentration measured at least one month apart. Eruptive xanthoma may be used as a surrogate for high TG levels (rare). ^b Secondary factors include alcohol, diabetes, metabolic syndrome, hypothyroidism, corticotherapy and additional drugs [6]. ^c If diagnosis is made during pregnancy, a second assessment is necessary to confirm diagnosis post-partum.

We initially tested the eight-item FCS score in two cohorts of 29 patients (see Methods in Ref. [41]). Sensitivity was estimated in an FCS cohort and specificity was tested in an MCS cohort (Figs. 3, 4A and B and Ref [41] Table 1).

The ability of the score to differentiate between FCS and MCS patients was subsequently tested in two independent replication Italian cohorts: the Rome Cohort (16 FCS and 15 MCS patients) and the Palermo Cohort (eight FCS and eight MCS patients) (Fig. 4C and D) [41]. The receiver operating characteristic (ROC) curve identified the best cut-off corresponding to an FCS score of ≥10 (area under the ROC curve 0.91). Within the FCS replication cohorts, sensitivity (87.5%) was similar in the Palermo and Rome cohorts; however, specificity tended to be lower in the Rome cohort than in the Palermo cohort (87.5% vs 66.6%) (Fig. 5). Taking into account all the patients studied, the overall sensitivity was 88% (95% confidence interval: 0.97, 0.76) with an overall specificity of 85% (95% confidence interval: 0.94, 0.75).

3.3. Discussion on diagnosis

A clinical diagnosis scoring system seems to be the best approach to improve diagnosis of FCS. It would particularly facilitate the diagnosis of FCS in countries or areas where genetic testing is unavailable despite its decreasing costs.

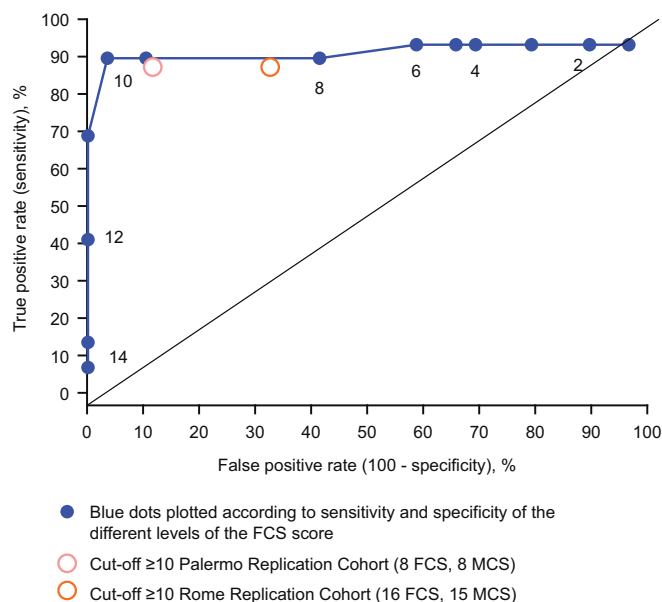


Fig. 5. Sensitivity and specificity of the FCS score. Receiver operating characteristic curve of the FCS score. FCS, familial chylomicronaemia syndrome; MCS, multifactorial chylomicronaemia syndrome.

needed. The FCS score might constitute a valuable tool for national and international registries, since it provides a way to take into account the differences in expressivity of the disease [22,42].

3.4. Treatment goals

The FCS score is a diagnostic tool. It should not be considered conditional for new-generation treatments. The indication of such treatments implies the assessment of the burden of the disease and especially the risk of recurrent hypertriglyceridaemic pancreatitis. The major aim of treatment for FCS is to reduce the risk of AP. Any management strategy should always aim to prevent pancreatitis events, which are characterised by marked increases in patient morbidity and mortality in FCS. Despite the fact that not all patients with HTG due to FCS develop pancreatitis, no biomarker is currently available to predict the risk of developing pancreatitis. Consequently, prevention of the occurrence of HTG remains the only valid target to avoid new episodes of pancreatitis.

TG levels <10 mmol/L (<885 mg/dL) are the most appropriate marker to reduce the risk of new episodes of AP. We suggest testing at least four times per year directly following pancreatitis in unstable patients and at least twice a year in stable patients without a history of HTG-induced pancreatitis. Blood withdrawal at the end of the afternoon [43] in the post-prandial state may be an option to challenge an apparently safe fasting plasma TG concentration. A strict hypolipidic diet remains the cornerstone of treatment but is often insufficient to avoid decompensation and recurrences of AP [2]. Since the majority of the TG-lowering interventions mediate their effect at least partially via LPL-mediated TG clearance, routine TG-lowering interventions are ineffective in FCS, including fibrate therapy and fish oil supplementation. Following the market withdrawal of the LPL gene therapy alipogene tiparvovec, current therapeutic options being investigated in FCS include apolipoprotein C3 antisense oligonucleotides (ASOs) [26,44] and angiopoietin-like 3 ASOs or monoclonal antibodies [45–47].

4. Data gaps

4.1. Areas requiring further attention

For patients with FCS, their symptoms, such as abdominal pain, fatigue and the ability to engage in daily activities, disease complications and adherence to a fat-restricted diet have an impact on their quality of life [48]. In a recent web-based survey of 60 US patients with FCS, a range of symptoms across the physical, emotional and cognitive domains were found to contribute to the burden of this illness [31]. More information is needed on how to reduce the handicap on social, work and family life due to abdominal pain, stress and strict diet restriction.

Since HTG has been found to correlate with decreased cognitive function in some but not all epidemiological studies [49,50], evaluating cognitive function in FCS with appropriate tools such as the Cambridge Neuropsychological Test Automated Battery could be considered [51].

Further investigation of the relationship between diet and pancreatitis is warranted. In addition to genetic factors, which need to be further identified [52–55], dietary factors related to pancreatitis, beyond those strictly related to TG levels such as alcohol, might be involved and could be a target. The mechanisms by which high levels of chylomicrons increase the risk of pancreatitis are not fully understood. Increased blood viscosity and impaired blood flow and peroxidative susceptibility causing pancreatic ischaemic and oxidative injury have been proposed as key factors [56,57]. Better understanding of these processes might create some translational opportunities.

5. Conclusions

Improvement of diagnosis of FCS is an important challenge in order to identify patients with the most severe form of HTG and with the highest risk of AP. Due to the strong similarities of the phenotype between FCS (considered as the recessive mono/bigenic disorder) and MCS (oligo/polygenic), the FCS score presented here provides a clinical tool able to discriminate between most cases. It offers the opportunity to focus genetic assessment in a targeted sub-population of hyperchylomicronaemic patients.

Conflicts of interest

PM has received fees paid to his institution for membership of advisory boards and clinical trials for Akcea/Ionis, Aegerion, Amgen, AMT/Chiesi, MSD, Novartis, Regeneron and Sanofi. RD has received honoraria for consulting from Amgen, Sanofi/Regeneron and Akcea/Ionis. MAV has received honoraria for membership of advisory boards and Speaker Bureaus for Akcea/Ionis, Aegerion, Amgen, MSD, Regeneron and Sanofi. MAr has received honoraria for membership of advisory boards and Speaker Bureaus for Akcea/Ionis, Aegerion, Amgen, Regeneron and Sanofi. ABC has received honoraria for Speaker Bureaus for Alpha-Sigma, Aegerion, MSD and Sanofi. DN has received honoraria for lectures from MSD and Sanofi. LD'E has received grants from Aegerion/Amryt. ADC has nothing to declare. CM has nothing to declare. LAA-SW has received honoraria for Speaker Bureaus and lectures for Amgen, Regeneron/Sanofi, Sanofi-Aventis, MSD, Pfizer, Bayer, Ferrer, Esteve and Rovi, and consultancy fees for Akcea, MSD, Pfizer and Rovi. MB has received honoraria for Speaker Bureaus for Abbott/Mylan, Abbott Vascular, Actavis, Akcea, Amgen, Biofarm, KRKA, MSD, Sanofi-Aventis, Valeant and Zentiva, consultancy fees for Abbott Vascular, Akcea, Amgen, Daichii Sankyo, Esperion, Lilly, MSD, Resverlogix and Sanofi-Aventis, and grants from Sanofi and Valeant. JB has received research grants from Amgen, AstraZeneca, NovoNordisk, Pfizer and

Regeneron/Sanofi, and honoraria for consultancy and lectures from Amgen, AstraZeneca, Eli Lilly, Merck, NovoNordisk, Pfizer and Regeneron/Sanofi. RC has presented data and chaired a meeting for Akcea, been on an advisory panel for Novartis, and is a trustee for HEART UK, The Cholesterol Charity. IG-B has received honoraria for consulting from Amgen, Sanofi, Eli Lilly, Regeneron, Akcea and Aegerion. EH reports personal fees from Akcea, outside the submitted work. CJ has received honoraria for consulting from Mylan, Abbott, UniQure and Akcea. XP has been involved in advisory boards with Amgen, Sanofi, Rubió, Ferrer and Esteve, has received honoraria from Akcea, and has given lectures for Mylan and Rubió. ZR has received honoraria for consulting from Akcea. JRvL has received honoraria from Akcea and grants from Aegerion/Amryt. HS reports personal fees from Akcea Therapeutics UK Ltd, during the conduct of the study, and grants and personal fees from Akcea Therapeutics UK Ltd, Amgen, Sanofi, Alexion Pharmaceuticals and Chiesi, outside the submitted work. CS has nothing to disclose. ES reports lecturing fees paid to his institute by Amgen, Sanofi, Chiesi, AstraZeneca, Regeneron and Akcea. EB declares having received honoraria for consulting/presentation from AstraZeneca, Amgen, Genfit, MSD, Sanofi, Regeneron, Unilever, Danone, Aegerion, Chiesi, Rottapharm-MEDA, Lilly, Ionis Pharmaceuticals and Akcea.

Financial support

The expert panel was initiated and supported by Akcea Therapeutics. The concepts addressed in this article were originally discussed at a meeting convened by Akcea for which participants, including some of the authors of this publication, received an honorarium. However, the authors received no payment in relation to the development of this publication, which was developed separately from the meeting. Akcea had no role and no support in the studies leading to establishment of the FCS score and did not interfere with the writing of the manuscript, except for funding editorial support.

Author contributions

The authors meet the criteria for authorship as recommended by the International Committee of Medical Journal Editors. They take full responsibility for the scope, direction, content of, and editorial decisions relating to the manuscript. The issues regarding FCS were discussed by PM, RD, MAV, MAR, LAS, MB, JB, RC, IGB, EH, CJ, XP, ZR, JRvL, HS, CS, ES and EB. The data for establishing the FCS score were generated and collected by RD, MAR, MAV, ABC, DN, LDE, ADC, CM and PM. The discussion regarding the topic was contributed to by RD, MAR, MAV, PM, ES and EB. The data were analysed by RD, MAR, MAV, PM and EB. The manuscript was written by PM and EB. All authors reviewed the manuscript.

Acknowledgements

Medical writing assistance was provided by Karen Brayshaw, PhD, of Complete HealthVizion, which was contracted and compensated by Akcea Therapeutics.

We thank Marine Ginoux from Pharmaco Epidémiologie Lyon for providing assistance in the establishment of the ROC curve.

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